

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
DIKEGULAC SODIUM

Chemical Code # 002004, Tolerance # 50535
SB 950 # 279

Original date: 4/20/99

I. DATA GAP STATUS

Chronic, rat	Data gap, no study submitted ¹
Chronic toxicity, dog:	Data gap, no study submitted ¹
Oncogenicity, rat:	Data gap, no study submitted
Oncogenicity, mouse:	Data gap, no study submitted
Reproduction, rat:	Data gap, no study submitted
Teratology, rat:	Data gap, inadequate study, no adverse effect indicated
Teratology, rabbit:	Data gap, inadequate study, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	Data gap, no study submitted
Neurotoxicity:	Not required at this time.

¹ Subchronic studies

Toxicology one-liners are attached.

All record numbers through 141804 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T990420

Original by: J.S. Kishiyama and Gee, April 20, 1999

Dikegulac sodium is used as a plant growth regulator.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT

No study submitted.

Subchronic:

019 137923 Hummler, H. "Tolerance Experiment on Rats with Oral Administration of Ro 07-6145/001 (DAG) for 13 Weeks". Roche Corporate Laboratory, Laboratory Project ID B-85 589. November 11, 1975. Ro 07-6145/001 (DAG), purity and lot number not stated, was administered admixed with the feed at concentrations of 0, 200, 700, and 2000 mg/kg for 13 weeks to 22 Füllinsdorf albino rats/sex/group (equivalent to a mean daily intake of: M: 202, 709 and 2008 mg/kg/day; F: 206, 710 and 2028 mg/kg/day). The author reported no treatment-related effects. NOEL = 700 mg/kg (lower body weight in males at 2000 mg/kg). UNACCEPTABLE but possibly upgradeable (purity and analysis of dosing material, husbandry information, method used to select animals for clinical chemistry/hematology and randomization). (Kishiyama and Gee, 2/10/99).

007 987694 Hummler and Halder "Orientation tolerance study in rats after oral administration for 6 weeks." (Hoffmann-LaRoche, 1/21/74) Five per sex Fullinsdorf albino rats were fed 0, 700 or 2000 mg/kg b. wt.. for a total of 6 weeks. DAG was fed as the free acid weeks 1 - 3 and as the sodium salt, weeks 4 - 6. Body weights, food consumption and limited clinical chemistry parameters were determined. No effects were reported. SUPPLEMENTAL. No worksheet. (Gee, 4/20/99)

CHRONIC TOXICITY, DOG

No study submitted.

Subchronic:

019 137929 Hummler, H. "Tolerance Experiment on Dogs with Oral Administration of Ro 07-6145/001 (DAG) for 13 Weeks". Roche Corporate Laboratory, Laboratory Project ID B-85 589. November 11, 1975. Ro 07-6145/001 (DAG), purity and lot number not stated, was administered at concentrations of 0, 500 and 1200 via gelatin capsules and 3000 mg/kg via stomach tube for 13 weeks to 4 beagle dogs/sex/group. The author reported no treatment-related adverse effects. NOEL = 500 mg/kg/day (clinical sign of diarrhea). UNACCEPTABLE but possibly upgradeable (purity and characterization of the test material, analysis of the dosing material, method used to prepare the test material including capsules not described and negative control not adequately described, individual clinical signs and when occurred). (Kishiyama and Gee, 2/10/99).

007 072033 Paul, S. "Orientation tolerance study with Ro 7-6145/000 (DAG) in the dog." (Hoffmann-LaRoche, 11/27/73) One male and one female dog [from Fullinsdorf animal farm], between 10 - 12 months of age, were given doses in capsules raised from 50 to 1600 mg/kg/day and by gavage to 5000 mg/kg/day over 6 weeks [free acid form, purity not stated]. Limited hematology, clinical chemistry, urinalysis, ophthalmology and histopathology were performed. No signs were noted up to 4000 mg/kg/day. Apathy, increased vomiting and watery stools were noted the last week. The only histological effect reported was severe vacuolation of the cytoplasm of liver cells. No control dogs. No worksheet. SUPPLEMENTAL. (Gee, 4/20/99)

007 072034 Paul, S. "Orienting tolerance study with Ro 7-6145/001 (DAG) in the dog." DAG as sodium salt was given to 1 male and 1 female dog [Fullinsdorf animal farm] at doses raised from 500 mg/kg to 20 g/kg over 5 weeks by stomach tube. Limited hematology, clinical

chemistry, urinalysis, ophthalmology and histopathology were performed. Diarrhea and vomiting were reported toward the end of the study. Alkaline phosphatase was increased and cholesterol was lower but no controls were included. No worksheet. SUPPLEMENTAL. (Gee, 4/20/99).

ONCOGENICITY, RAT

No study submitted.

ONCOGENICITY, MOUSE

No study submitted.

REPRODUCTION, RAT

No study submitted.

TERATOLOGY, RAT

003 28360 Backes, G. "Embryotoxic Studies in the Rat following Oral Administration of Ro 07-6145/001". (Hoffmann-LaRoche, 2/9/77.) Dikegulac sodium, lot BZ 1455 - no purity stated [see 022, 141803] was administered via gavage at concentrations of 0 (distilled water), 200, 700 or 2000 mg/kg to 30-40 mated female Füllinsdorf albino rats/group during gestation days 7 through 16. Approximately one-half the number of females/group were allowed to deliver. Fetuses from ten dams were examined for skeletal effects and from seven dams by the Wilson technique. Pups from dams which littered were examined on days 1, 4, 12 and 23 postpartum for weight and mortality. Pups from eight litters were necropsied and weights of the heart, liver and kidneys determined. A statement was made that dams at 2000 mg/kg showed "light sedation" on the first two days of dosing - incidence was not reported. No adverse developmental effects were reported. Nominal maternal NOEL = 7mg/kg (sedation) and developmental NOEL = 2000 mg/kg/day. UNACCEPTABLE (Test article characteristics not reported; number of animals for developmental portion (17, 17, 18 and 17 in control through high dose), number of fetuses examined for skeletal (approximately 10 litters) and for visceral (seven litters) effects, rat strain justification, individual clinical observations at the high dose). (A. Apostolou, 7/16/85; Gee, 2/10/99).

TERATOLOGY, RABBIT

003 028359 Backes, G. "Embryotoxic Studies in the Rabbit following Oral Administration of Ro 07-6145/001". (Hoffmann-LaRoche, 4/20/77.) Dikegulac sodium, lot BZ 1455, no purity stated [see 022, 141803], was administered via gavage at concentrations of 0 (distilled water), 200, 700 or 2000 mg/kg to 20 Yellow-silver mated female rabbits/group during gestation days 7 through 19. Slight effect on bodyweight and diarrhea were observed for high dose does. Skeletal exams were by x-ray or Alizarin-red staining. No adverse developmental effects reported. Nominal maternal NOEL = 700 mg/kg; developmental NOEL = 2000 mg/kg. UNACCEPTABLE (test article not characterized with no analyses of actual concentration. Possibly upgradeable. (A. Apostolou, 7/6/85; Gee, 2/10/99).

022 141803 Armbruster, J. A. "Supplemental Test Substance Purity Information for Embryotoxicity Studies in the Rabbit Following Oral Administration of Ro 07-6145/001" (supplements MRID 43064618). Roche Corporate Laboratory, Lab Project ID: none. April 12, 1995. The author compiled information on dikegulac compounds including the sodium salt of

dikegulac which was mentioned as the test article in many of the studies. Page 13 listed the purity of 8 lot numbers with a date of 5/5/75. Sodium salt of Dikegulac is a spray dried white powder from Nutley Lot No. 001122 identified with Ro numbers 07-6145/001, purity 98%, and stability for 3 years. No worksheet. (Kishiyama and Gee, 2/10/99).

022 141804 Armbruster, J. A. "Historical Control and Other Supplemental Information for Embryotoxicity Studies in the Rabbit Following Oral Administration of Ro 07-6145/001 (supplements MRID 43064618)". Roche Corporate Laboratory, Laboratory Project ID: none. April 12, 1995. The author put emphasis on not mis-interpreting the presence of cysts in the brain. The author addressed the historical (1984-1994) incidence of cysts in the medulla oblongata for the Swiss-Hare rabbit strain (1989: 7 of 83 fetuses); Note: Hoffmann La Roche in about 1980 replaced the Fullinsdorf Yellow-Silver strain with the Swiss-Hare strain. The author also cited two journal articles that concluded cysts in brains of rabbits arise easily and are fixation-induced artifacts. In record No. 028359, the incidence of "cysts" was 2 fetuses in 1/15 litters at 2000 mg/kg and 0/16 in controls. Citations: Niggeschulz, A, *et al.*, Arch. Toxicol. 37: 227-232 (1977). "Fixation-induced cyst-like spaces in the brains of rabbit foetuses." Joosten, H. F. P. *et al.*, Arch. Toxicol. 47: 25-37 (1981). "Cysts in rabbit foetal brains." No work sheet. (Kishiyama and Gee, 2/10/99).

GENE MUTATION

003 028488 Schüpbach, M. "Mutagenicity Testing with Ro 7-6145/001, Results of *In Vitro* Trial with *Salmonella typhimurium* and the Host-Mediated Assays". (Hoffmann - La Roche Inc. 6/22/76.) Dikegulac sodium (no characterization) was administered via single gavage at doses of 500, 1500, or 2500 mg/kg to 1 to 3 Füllinsdorf albino mice/sex/dose and, at the same time, a single I.P. (2 ml suspension) injection of *Salmonella typhimurium* strains TA 1964, TA 1530, TA1531, or TA1532. The cells were recovered 3 hours later from the peritoneal cavity and plated. *In vitro* testing was done at 2 mg/dish added to 2 dishes. No increase in revertants was reported. UNACCEPTABLE and not upgradeable (study lacks information on: test article characterization, positive control, individual data and more than one concentration *in vitro*). (A. Apostolou, 7/16/85).

002 and 003 28354. Summary of 003 028488.

002 028355 and 028356. Summary of 028488.

** 022 141762 Lawlor, T. E. "Mutagenicity Test with Dikegulac Sodium Technical in the *Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay". Corning Hazleton Inc., (CHV), Laboratory Project ID CHV Study No.: 17008-0-409. October 11, 1995. Dikegulac Sodium Technical, 98%, was evaluated for mutagenicity at concentrations of 0, 100, 333, 1000, 3330 and 5000 µg/plate, in triplicate in the absence and presence of rat liver S9 Mix using *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA. Dikegulac sodium treatment did not significantly increase the number of revertants in *Salmonella typhimurium* and *Escherichia coli* tester strain(s). ACCEPTABLE. (Kishiyama and Gee, 2/9/99)

022 141785 Cifone, M. A. "Mutagenicity Test on Dikegulac Sodium Technical in the L5178Y+/- Mouse Lymphoma Forward Mutation Assay". Corning Hazleton Inc., (CHV), Laboratory Project ID CHV Study No.: 17008-0-431. September 26, 1995. Dikegulac Sodium Technical, 98%, was evaluated for mutagenicity at concentrations of 0, 500, 1000, 2000, 3000, 4000, or 5000 µg/ml using the mouse lymphoma L5178Y+/- cell line with and without rat liver S9 activation with 4-hour exposure and a two-day expression period. Only one trial was run. Report states that since the results were considered negative, colonies were not sized. Mutation frequency was not increased significantly with dikegulac sodium. Positive controls were functional. UNACCEPTABLE (no repeat trial and no individual plate counts). (Kishiyama and Gee,

2/10/1999)

CHROMOSOME EFFECTS

003 028487 Schüpbach, M. "Mutagenicity Testing with Ro 7-6145/001, II. Results of the Micronucleus Test of The Bone Marrow Cells of the Mouse". (Hoffmann - La Roche Inc. 7/2/76.) Dikegulac sodium was administered via i.p. (2x) injections at doses of 0 (0.1 ml physiological saline), 500, 1500, or 2500 mg/kg to 3 Füllinsdorf albino mice/sex/dose group. Bone marrow was sampled one time, 6 hours after the 2nd treatment. No increase in micronuclei reported. UNACCEPTABLE and not upgradeable (deficiencies: no test article characterization, too few animals, dose selection not justified, single sampling time, no positive control, criteria for scoring not reported). (A. Apostolou, 7/17/85).

002 and 003 028354. Summary of 003 028487.

002 028357. Summary of 003 028487.

** 022 141783 Murli, H. "Mutagenicity Test with Dikegulac Sodium Technical in an *In Vivo* Mouse Micronucleus Assay". Corning Hazleton Inc., Laboratory Project ID CHV Study No.: 17008-0-455. September 22, 1995. Dikegulac Sodium Technical, 98%, was administered via a single gavage at doses of 0 (deionized water), 1250, 2500, or 5000 mg/kg to 5 Crl:CD-1®(ICR) BR mice/sex/group/harvest time (24, 48, or 72 hours). No significant increase in micronucleated polychromatic erythrocytes with dikegulac sodium treatments was reported. Cyclophosphamide was used as the positive control at 24 hours and was functional. ACCEPTABLE. (Kishiyama and Gee, 2/9/1999) .

003 028486 Schüpbach, M. and H. Hummler. "Mutagenicity Testing with Ro 07-6145/001, III. Dominant-Lethal Test in Mice". (Hoffmann - La Roche Inc. 3/22/77). Dikegulac sodium was administered via oral gavage for 5 days at concentrations of 1000 or 3000 mg/kg and a one-time treatment at 10000 mg/kg to 25 male Füllinsdorf strain mice/dose group. Males were mated to two untreated females for six days with ten repeats. Females were autopsied 12 days after removal from males. No treatment-related increase in dominant lethals reported. UNACCEPTABLE (deficiencies: no test article characterization, no positive control data). (A. Apostolou, 7/17/85).

002 and 003 028354. Summary of 003 028486.

DNA DAMAGE

No study submitted.

NEUROTOXICITY

Not required at this time

MISCELLANEOUS

022 141795 Teeter, D. and M. A. Morrissey. "Purity Determination of Dikegulac - Sodium (Sodium Salt of 2,3:4,6-bis-o-(1-methylethylidene)- α -L-xylo-2-hexulofuranosonic acid)". Corning Hazleton Inc., Project No. CHW 6384-131. September 20, 1995. The purity from the analysis of eight replicates of dikegulac sodium technical (Lot 94-535-68-06) by HPLC was determined to be 98.0% (S.D. ± 0.58). This lot no. was used in several genotoxicity studies in volume -022. No work sheet. (Kishiyama and Gee, 2/10/99).

022 141802 Wipf, H. K. "Na-DAG (Ro 07-6145/001): Stability in Aqueous Solution." Roche Corporate Laboratory, lab Project ID: none. March 19, 1974. Na-DAG (Ro 07-6145/001) in aqueous solution was stable at room temperature [20 °C] providing the solution was neutral or basic. Testing was done at 20 °C and 50°C, pH 4, 7 or 10. Determination of DAG by GC, No hydrolysis was found over 31 days at pH 7 (20°C) or pH 10 (20 and 50°C). No work sheet. (Kishiyama and Gee, 2/10/99).